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Synthesis, Characterization, *in vitro* Antimicrobial Evaluation and *in silico* Molecular Docking and ADME Prediction of 4-Chlorophenyl Furfuran Derivatives bearing Pyrazole Moieties

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A series of 1-(5-(5-(4-chlorophenyl)furan-2-yl)-4,5-dihyropyrazol-1-yl ethanone (**5a-h**) was synthesized through *E*-(3-(5-(4-chlorophenyl)furan-2-yl)-1-phenylprop-2-en-1-one (**3a-h**) with hydrazine monohydrate and sodium acetate. Totally, eight compounds were synthesized and their structures were elucidated by infrared, ^{1}H & ^{13}C NMR, elemental analysis, antimicrobial studies, *in silico* molecular docking studies and also *in silico* ADME prediction. Antimicrobial studies of the synthesized compounds showed good to moderate activity against the all the stains compared with standard drugs. *in silico* Molecular docking study was carried out using bacterial protein and BC protein. Synthesized compounds (**5a-h**) showed good docking score compared with ciprofloxacin. Antimicrobial study was carried out for 4-chlorophenyl furfuran pyrazole derivatives (**5a-h**). The results of assessment of toxicities, drug likeness and drug score profiles of compounds (**5a-j**) are promising.

Keywords: 4-Chlorophenyl furfuraldehyde, *in silico* Molecular docking, *in silico* ADME property, Antimicrobial activity.

INTRODUCTION

Now a day, there has been a growing interest to synthesis of bioactive compounds in the field of organic chemistry. The chalcones and their derivatives are important intermediates in organic chemistry [1-4]. The most important function of chalcones is to build up a variety of heterocyclic compounds of physical importance. Due to the presence of enone functionality in chalcone, moiety confers antimicrobial [5-7], anti-inflamatory [8], antimalarial [9,10], antileithshmanial [11], antioxidant [12], antitubercular [13,14], anticancer [15-17] and their biological activities [18,19]. Among the nitrogen containing hererocyclic compounds pyrazole apparently gained considerable importance owing to their varied biological properties and therapeutic importance. These types of compounds have various physical, chemical and biological properties [20] spanning a broad spectrum of reactivity and stability. Heterocyclic compounds widely occur in nature and play a vital role in metabolism because their structural sub-units are present in many natural products, including vitamins, antibiotics, hormones, and alkaloids as well as agrochemicals dyes [21].

Pyrazoles are widely used as core motifs for a large number of compounds for various applications in medicine. In medicine pyrazole is found as a pharmacophore in some of the biological molecules [22]. Pyrazole derivatives are the most important derivatives in pharmaceutical industries because of the heterocyclic compounds containing nitrogen and possessing good biological activities that are antidiabetic [23], anticonvulsant [24], anticancer [25-27] and antimicrobial [27,28].

Molecular docking may be defined as an optimization problem, which would describe the "best-fit" orientation of a ligand that binds to a particular protein of interest and is used to predict the structure of the intermolecular complex formed between two or more molecules. The most important interesting case is the protein ligand interaction, because of its applications in medicines. Ligand is a small molecule, which interact with protein binding sits. There are several possible mutual conformations in which binding may occur. These are commonly called binding modes [29-31]. In modern drug designing, molecular docking is routinely used for understanding drug-receptor interaction. Molecular docking provides useful information about drug receptor interactions and is frequently used

to predict the binding orientation of small molecule drug candidates to their protein targets in order to predict the affinity of the small molecule.

The QSAR/QSPR community has, for a good number of years, developed models for the prediction of physiochemical properties of interest in ADMET (absorption, distribution, metabolism, excretion and toxicity). These include partition coefficient, aqueous solubility [32], absorption and permeability [33], blood brain barrier (BBB) penetration [33], plasma protein binding [33], metabolism [34], hERG inhibition [35], excretion [36], P-glycoprotein (P-gp) efflux, physiologically based pharmacokinetic (PBPK) modelling and toxicity [37,38]. In addition of course, pharmacophore and homology modelling have also proceeded, to allow improve prediction of metabolism and toxicity [39,40]. Today, the tests that make up ADMET evaluation are low throughput and apparently not informative or accurate enough to predict drug′s probability of success; given the high failure rate of compounds at all stages of development [41]. Drug discover companies are therefore seeking to reorganize the ADMET process, advancing the chain of early discovery. The objectives is to predict, early in the process perhaps even before the compounds are synthesized, which compounds pass the test for the good drug. Over the past few years, much software has been developed for the properties and toxicity of ADME-based organism [42,43]. We have to predict the ADME properties for the online software swissADME and Molinspiration online toolkit.

The main focus of this work is design and synthesis of novel 4-chlorophenyl furfural pyrazole derivatives, which have not been previously reported. The target compound′s structure was elucidated using FT-IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis. Finally, all of them have to investigate their biological evaluation and ADME prediction. *in silico* Molecular docking study was carried out using BC protein and bacterial protein.

EXPERIMENTAL

The chemicals and reagents for synthesis were procured from Hi-Media and Sigma Aldrich, Mumbai, India. Melting points were measured in open capillary tubes on a MELT-TEMP apparatus and are uncorrected. The elemental analyses (C,H,N) were performed using the Perkin-Elmer 2400 CHN analyzer. Analyses indicated by the symbol of the elements are functions were within ± 0.5 % of the theoretical values. IR spectra are recorded in KBr (pellet forms) on a Shimadzu IR Spectrometer and noteworthy absorption values (cm^{-1}) alone are listed. ^{1}H & ^{13}C NMR spectral data were recorded at 400 MHz and 100 MHz, respectively using $CDCl_3$ as solvent and trimethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm units with use of δ scale. Performing TLC assessed the reactions and the purity of the products. By adopting the literature precedent [17], chalcones (**3a-h**) were prepared.

Synthesis of 1-(5-(5-(4- chlorophenyl)furan-2-yl)-4,5-dihydropyrazol-1-yl ethanone (5a-h): Furfural chalcones (**3a-h**), (0.01 mol), hydrazine hydrate (0.01 mol), anhydrous sodium acetate (0.01 mol) and acetic acid (30 mL) were taken in a round bottom flask and the reaction mixture was refluxed until the products formed. The reaction was monitored by TLC. The reaction mixture was poured into crushed ice and left overnight. The precipitate was separated by filtration, washed well with water, dried and the obtained solids were purified by column chromatography using chloroform and ethylacetate (1:1) mixture as eluent, which afford the title compounds (**5a-h**) in good yields.

Spectral data

1-(3-(5-(4-Chlorophenyl)furan-2-yl-4,5-dihydropyazole-1-yl)ethanone (5a): Yield: 86%; m.p.: 256-258 ºC; yellow solid; m.f.: $C_{21}H_{17}N_2O_2Cl$. Elemental analysis calcd. (found) %: C, 69.07 (69.14); H, 4.65 (4.70); N, 7.67 (7.67): IR (KBr, ν_{max}, cm^{-1}): Pyrazole ring 1514.18 (C=N), 1663.07 (C=O), 3030-3028 (aromatic CH *str.*), 2971-2942 (aliphatic CH *str.*); ^{1}H NMR ($CDCl_3$) 400 MHz, δ ppm: 3.51 (1H, dd, H_{4a}, $J_{4a,4e}$ = 5 Hz, $J_{4a,5a}$ = 18.2 Hz); 3.77 (1H, dd, H_{4e}, $J_{4e,4a}$ = 18 Hz, $J_{4e,5a}$ = 12 Hz); 5.68 (1H, dd, H_{5a}, $J_{5a,4a}$ = 12 Hz, $J_{5a,5e}$ = 4.6 Hz); 6.44 ($C_{3'}$ & $C_{4'}$ of furan ring, 1H, d, J = 3.2 Hz), 2.29 (3H, s, acetyl methyl proton), 7.31-7.90 (9H, m, Ar-H). ^{13}C NMR, δ ppm: 167.72 (acetyl carbonyl), 164.52 (C-3 of pyrazole ring), 38.51 (C-4 of pyrazole ring), 53.37 (C-5 of pyrazole ring), 107.35 (C-3′ of furan ring), 109.33 (C-4′ of furan ring), 115.76-128.98 (Ar-C), 21.72 (acetyl methyl carbon), 129,131.73 (*ipso* carbons).

1-(3-(5-(4-Chlorophenyl)furan-2-yl)-5-(4-fluorophenyl)-4,5-dihydropyrazole-1-yl) ethanone (5b): Yield 80%; m.p.: 268-270 ºC; yellow solid; m.f.: $C_{21}H_{16}N_2O_2ClF$. Elemental analysis calcd. (found) %: C, 65.89 (65.89); H, 4.17 (4.21); N, 7.31 (7.32): IR (KBr, ν_{max}, cm^{-1}): Pyrazole ring 1544.98 (C=N), 1647.21 (C=O), 3095.75 (aromatic CH *str.*), 2981, 2996 (aliphatic CH *str.*);^{1}H NMR ($CDCl_3$) 400 MHz δ ppm: 3.52 (1H, dd, H_{4a}, $J_{4a,4e}$ = 4.8 Hz, $J_{4a,5a}$ = 18 Hz); 3.77 (1H, dd, H_{4e}, $J_{4e,4e}$ = 17.8 Hz, $J_{4e,5a}$ = 12 Hz); 5.65 (1H, dd, H_{5a}, $J_{5a,4a}$ = 12 Hz, $J_{5a,4e}$ = 4.8 Hz); 6.44 ($C_{3'}$ & $C_{4'}$ of furan ring 1H, d, J = 3.2 Hz); 2.28 (3H, s, acetyl methyl proton), 7.02-7.91 (8H, m, Ar-H). ^{13}C NMR δ ppm: 167.70 (acetyl carbonyl), 164.43 (C-3 of pyrazole ring), 35.50 (C-4 of pyrazole ring), 63.51 (C-5 of pyrazole ring), 107.34 ($C_{3'}$ of furan ring), 109.11 ($C_{4'}$ of furan ring), 113.96-133.48 (Ar-C), 22.32 (acetyl methyl carbon), 130, 142 (*ipso* carbons).

1-(5-(4-Bromophenyl-3-(5-(4-chlorophenyl)furan-2-yl)-4,5-dihydropyrazole-1-yl) ethanone (5c): Yield 78%; m.p.: 286-288 ºC; yellow solid; m.f.: $C_{21}H_{16}N_2O_2BrCl$. Elemental analysis calcd. (found) %: C, 56.59 (56.84); H, 3.60 (3.63); N, 6.31 (6.31). IR (KBr, ν_{max}, cm^{-1}): Pyrazole ring 1585.15 (C=N), 1643.35 (C=O), 3066.11 (aromatic CH *str.*), 2988, 2884 (aliphatic CH *str.*); ^{1}H NMR ($CDCl_3$) 400 MHz δ ppm: 3.52 (1H, dd, H_{4a}, $J_{4a,4e}$ = 4.4 Hz, $J_{4a,5a}$ = 18.2 Hz), 3.74 (1H, dd, H_{4e}, $J_{4e,4a}$ = 17.8 Hz, $J_{4e,5a}$ = 12 Hz); 5.64 (1H, dd, H_{5a}, $J_{5a,4a}$ = 12 Hz, $J_{5a,4e}$ = 4.8 Hz), 6.42 ($C_{3'}$ & $C_{4'}$ of furan ring, 1H, d, J = 3.4 Hz); 2.28 (3H, s, acetyl methyl proton), 7.02-7.77 (8H, m, Ar-H).^{13}C NMR δ ppm; 167.47 (acetyl carbonyl), 160.97 (C-3 of pyrazole ring), 38.52 (C-4 of pyrazole ring), 53.10 (C-5 of pyrazole ring), 107.33($C_{3'}$ of furan ring), 109.21 ($C_{4'}$ of furan ring), 114.22-131.71 (Ar-C), 21.71 (acetyl methyl carbon), 142,144 (*ipso carbons*).

1-(3-(5-(4-Chlorophenyl)furan-2yl)-5-*p*-tolylphenyl)-4,5-dihydropyrazole-1-yl)ethanone (5d): Yield 82%; m.p.: 276-286 ºC; yellow solid; m.f.: $C_{22}H_{19}N_2O_2Cl$. Elemental analysis calcd. (found) %: C, 69.68 (69.75); H, 5.01 (5.05); N, 7.39

(7.39). IR (KBr, ν_{max}, cm^{-1}): Pyrazole ring 1510.26 (C=N), 1643.35 (C=O), 3024.30 (aromatic CH *str.*), 2990, 2984 (aliphatic CH *str.*); ^{1}H NMR ($CDCl_3$) 400 MHz, δ ppm: 3.54 (1H, dd, H_{4a}, $J_{4a,4e}$ = 5 Hz, $J_{4a,5a}$ = 18.2 Hz); 3.72 (1H, dd, H_{4e}, $J_{4e,4a}$ = 17.8 Hz, $J_{4e.5a}$ = 11.8Hz), 5.68 (1H, dd, H_{5a}, $J_{5a,4a}$ = 11.8 Hz, $J_{5a,4e}$ = 4.8 Hz); 6.44 ($C_{3'}$ & $C_{4'}$ of furan ring, 1H, d, J = 3.4 Hz), 1.36 (3H, t, methyl proton), 2.29 (acetyl methyl proton), 7.24-8.28 (8H, m, aromatic protons). ^{13}C NMR δ ppm: 167.75 (acetyl carbonyl), 162.87 (C-3 of pyrazole ring), 38.46 (C-4 of pyrazole ring), 53.15 (C-5 of pyrazole ring), 107.33 ($C_{3'}$ of furan ring), 109.27 ($C_{4'}$ of furan ring), 124.90-131.73 (Ar-C), 21.71 (acetyl methyl carbon), 20.99 (methyl carbon), 141, 144 (*ipso* carbons).

1-(3-(5-(4-Chlorophenyl)furan-2-yl)-5-(4-methoxy-4,5-dihydropyrazole-1-yl-ethanone (5e): Yield 76%; m.p.: 284-286 ºC; yellow solid; m.f.: $C_{22}H_{19}N_2O_3Cl$. Elemental analysis calcd. (found) %: C, 66.86 (66.92); H, 4.81 (4.85); N, 7.09 (7.09). IR (KBr, ν_{max}, cm^{-1}): Pyrazole ring 1533.23 (C=N), 1654.17 (C=O), 3048,3092 (aromatic CH *str.*), 2967, 2988 (aliphatic CH *str.*); ^{1}H NMR ($CDCl_3$) 400 MHz, δ ppm: 3.58 (1H, dd, H_{4a}, $J_{4a.4e}$ = 4.4 Hz, $J_{4a.5a}$ = 18 Hz); 3.78 (1H, dd, H_{4e}, $J_{4e,4a}$ = 17.8 Hz, $J_{4e,5a}$ = 11.8 Hz); 5.72 (1H, dd, $J_{5a,4a}$ = 11.8 Hz, $J_{5a,5e}$ = 4.6 Hz); 6.48 ($C_{3'}$ & $C_{4'}$ of furan ring,1H, d, J = 3.6 Hz); 2.26 (3H, s, acetyl methyl proton); 3.73 (methoxy proton); 7.33-7.98 (8H, m, Ar-H); ^{13}C NMR δ ppm: 167.89 (acetyl carbonyl), 163.39 (C-3 of pyrazole ring), 37.98 (C-4 of pyrazole ring), 53.68 (C-5 of pyrazole ring), 107.55 ($C_{3'}$ of furan ring), 109.25 ($C_{4'}$ of furan ring), 118.65-130.49 (Ar-C), 21.63 (acetyl methyl carbon), 55.32 (methoxy carbon), 140, 142 (*ipso* carbons).

1-(5-(4-Biphenyl-3-(5-(4-chlorophenyl)furan-2-yl)-4,5-dihydropyrazole-1-yl-ethanone (5f): Yield 78%; m.p.: 266-268 ºC; yellow solid; m.f.: $C_{27}H_{21}N_2O_2Cl$. Elemental analysis calcd. (found) %: C, 73.49 (73.55); H, 4.76 (4.80); N, 6.35 (6.35). IR (KBr, ν_{max}, cm^{-1}): Pyrazole ring 1512.81 (C=N), 1652.06 (C=O), 3088.3078 (aromatic CH *str.*), 2976, 2956 (aliphatic CH *str.*); ^{1}H NMR ($CDCl_3$) 400 MHz, δ ppm: 3.52 (1H, dd, H_{4a}, $J_{4a.4e}$ = 4.6 Hz, $J_{4a.5a}$ = 17.6 Hz); 3.75 (1H, dd, H_{4e}, $J_{4e,4a}$ = 18 Hz, $J_{4e,5a}$ = 12 Hz); 5.66 (1H, dd, $J_{5a,4a}$ = 12 Hz, $J_{5a,5e}$ = 4.8 Hz); 6.43 ($C_{3'}$ & $C_{4'}$ of furan ring , 1H, d, J = 3.6 Hz); 2.28 (3H, s, acetyl methyl proton); 7.12-8.24 (8H, m, Ar-H): ^{13}C NMR δ ppm: 167.53 (acetyl carbonyl), 164.72 (C-3 of pyrazole ring), 36.55 (C-4 of pyrazole ring), 55.74 (C-5 of pyrazole ring), 107.41 ($C_{3'}$ of furan ring), 109.42 ($C_{4'}$ of furan ring), 116.34-131.69 (Ar-C), 22.08 (acetyl methyl carbon), 144, 146 (*ipso* carbons).

1-(5-(4-Chlorophenyl)3-(5-(4-chlorophenyl)furan-2-yl)-4,5-dihydropyrazole-1-yl)ethanone (5j): Yield 84%; m.p.: 272-274 ºC; yellow solid; m.f.: $C_{21}H_{16}N_2O_2Cl_2$. Elemental analysis calcd. (found) %: C, 63.11 (63.17); H, 4.00 (4.04); N, 7.01 (7.02). IR (KBr, ν_{max}, cm^{-1}): Pyrazole ring 1519.03 (C=N), 1662.15 (C=O), 3089 (aromatic CH *str.*), 2968 (aliphatic CH *str.*); ^{1}H NMR ($CDCl_3$) 400 MHz, δ ppm: 3.56 (1H, dd, H_{4a}, $J_{4a.4e}$ = 4.8 Hz, $J_{4a.5a}$ = 17.8 Hz); 3.68 (1H, dd, H_{4e}, $J_{4e,4a}$ = 17.8 Hz, $J_{4e,5a}$ = 12 Hz); 5.72 (1H, dd, $J_{5a,4a}$ = 11.8 Hz, $J_{5a,5e}$ = 4.4 Hz); 6.46 ($C_{3'}$ & $C_{4'}$ of furan ring, 1H, d, J = 3.2 Hz); 2.29 (3H, s, acetyl methyl proton); 7.03-8.01 (8H, m, Ar-H); 167.72 (acetyl carbonyl carbon); 164.58 (C-3 of pyrazole ring), 38.45 (C-4 of pyrazole ring); 54.39 (C-5 of pyrazole ring), 107.35($C_{3'}$ of furan ring), 109.38 ($C_{4'}$ of furan ring), 118.90-131.34 (Ar-C), 21.99 (acetyl methyl carbon), 138, 142 (*ipso* carbon).

1-(3-(5-(4-Chlorophenyl-2-yl)-5-(4-nitrophenyl)-4,5-dihydropyrazole-1-yl-ethanone (5h): Yield: 68%; m.p.: 292-294 ºC; yellow solid; m.f. $C_{21}H_{16}N_2O_2Cl$. Elemental analysis calcd. (found) %: C, 65.82 (65.89); H, 4.17 (4.21); N, 7.31 (7.32). IR (KBr, ν_{max}, cm^{-1}): Pyrazole ring 1541.43 (C=N), 1632.11 (C=O), 3018 (aromatic CH *str.*), 2920-2899 (aliphatic *str.*); ^{1}H NMR ($CDCl_3$) 400 MHz, δ ppm: 3.52(1H, dd, H_{4a}, $J_{4a.4e}$ = 5.0 Hz, $J_{4a.5a}$ = 18 Hz); 5.78 (1H, dd, H_{4e}, $J_{4e,4a}$ = 18 Hz, $J_{4e,5a}$ = 12 Hz); 5.78 (1H, dd, $J_{5a,4a}$ = 12 Hz, $J_{5a,5e}$ = 4.8 Hz); 6.42 ($C_{3'}$ & $C_{4'}$ of furan ring,1H, d, J = 3.4 Hz). ^{13}C NMR, δ ppm: 2.28 (3H, s, acetyl methyl proton); 7.24-7.89 (8H, m, Ar-H); 167.71 (acetyl carbonyl carbon); 162.24 (C-3 of pyrazole ring); 37.24 (C-4 of pyrazole ring), 54.88 (C-5 of pyrazole ring), 107.38 ($C_{3'}$ of furan ring), 109.29 ($C_{4'}$ of furan ring), 117.23-131.02 (Ar-C), 21.23 (acetyl methyl carbon),138,140,144 (*ipso* carbons).

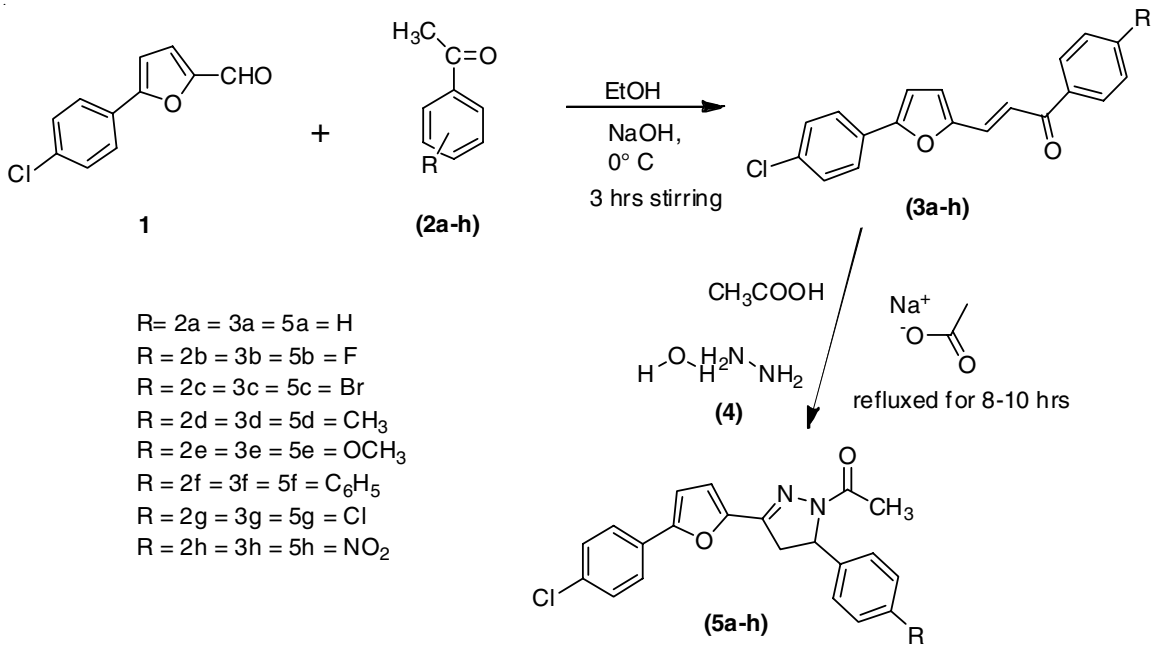
Antimicrobial screening: Antimicrobial study was carried out for synthesized 4-chlorophenyl furfural moiety pyrazole derivatives (**5a-h**) using agar disk diffusion method. The various bacterial strains *viz. S. aureus, E. coli, P. aeruginosa, S. pyogenes* and *Candida albicans* were used in this study. This activity was carried out with the sample concentration of 1 mg/mL and the zone of inhibition measured. The antimicrobial screening procedure was carried out by literature survey method [17].

Molecular docking: Molecular docking studies were carried out for synthesized 4-chlorophenyl furfural pyrazole derivatives using BC protein and bacterial protein by Auto dock version 4.2.5.1 docking software. The reference method was followed for the docking study [19].

***in silico* ADME properties:** Absorption, distribution, metabolism, and excretion (ADME) properties of all the synthesized 4-chlorophenyl furfural pyrazole derivatives (**5a-h**) were predicted using swissADME online tool and Molinspiration online software. This software tool provided information about the molecular weight, hydrogen bond acceptor, hydrogen bond donar, octanol water partition co-efficient (log $p^{c}_{0/w}$, solubility (log S), skin-permeation (log K_p), total polar surface area (TPSA), molar refractivity and bioavailability score.

RESULTS AND DISCUSSION

The novel 1-(5-(5-(4-chlorophenyl)furan-2-yl)-4,5-dihydro-3-phenyl pyrazol-1-yl)ethanone derivatives were synthesized from 3-(5-(4-chlorophenyl)furan-2-yl)-1-phenylprop-2-en-1-one derivatives. The chalcones were reacted with hydrazine monohydrate and acetic acid in presence of sodium ethanoate *via* nucleophilic cycloaddition reaction. The synthetic pathways are shown in **Scheme-I**. The synthesized compounds were characterized by the determination of their physico-chemical and spectral characteristics. The chemical structures of the synthesized furfuryl bearing pyrazole derivatives (**5a-g**) were established by ^{1}H/^{13}C NMR, FT-IR and elemental analysis. The IR spectrum of furfuryl bearing pyrazoles showed a characteristic band at 1663 cm^{-1} which indicated the presence of a amide carbonyl group group and a characteristic band at 1514 cm^{-1} for the presence of C=N functional group of pyrazole moiety. The absence of carbonyl band clearly supported the formation of compound **5a**, besides the disappearance of NH stretching vibration, which confirmed the *in situ* acylation reaction due



Scheme-I: Synthetic pathway for novel 4-chlorophenyl furfural bearing pyrazole derivatives (**5a-h**)

to acetic anhydride solvent. The bands at 3028 and 3030 cm^{-1} indicates the aromatic CH stretching frequencies.

The structures of furfuryl bearing pyrazoles were further confirmed by the corresponding ^1H NMR spectra. The ^1H NMR spectrum of compound **5a** shows the methylene protons (H-4a and H-4e) of the pyrazole moiety appeared as two doublets of doublets due to multiple coupling involving both *geminal* and *vicinal* protons. The signal for H-4a and H-4e were observed at 3.51 and 3.77 ppm, respectively. The doublet of doublet at 3.51 ppm was assigned to H4a proton of the pyrazole moiety. Likewise, the doublet of doublet at 3.77 ppm was assigned to H-4e proton of the pyrazole moiety. Similarly, methine proton (H-5) of pyrazoline is expected to give signal as a doublet of doublet due to *vicinal* coupling with two magnetically non-equivalent protons of the methylene group (H-4a and H-4e) of the pyrazoline moiety and the signals were observed at 5.68 ppm. Also, the acetyl methyl protons of pyrazoline moiety showed the signals as a singlet at 2.29 ppm. The furfuran ring has two protons; these two protons were appeared in the doublet at 6.44 ppm due to the presence of bulky groups such as pyrazole and electronegativity of chlorine present in the phenyl ring. The remaining signals at 7.31-7.90 ppm was due the presence of aromatic protons. In the ^{13}C NMR spectrum of 1-(3-(5-(4-chlorophenyl)furan-2-yl)-5-phenyl-4,5-dihydro-pyrazol-1-yl)-ethanone, ^{13}C resonance at 53.37 ppm was assigned to C-5 carbon of the pyrazole moiety. The ^{13}C resonance observed at 38.51 ppm was due to C-4 carbon of pyrazole moiety, while the ^{13}C resonance observed at 164.52 ppm was assigned to C-3 carbon of the pyrazole moiety. The ^{13}C resonance observed at 167.72 ppm was due the presence of acetyl carbonyl carbon and the ^{13}C resonance at 21.72 ppm was assigned to acetyl methyl carbon. The singnals observed at 107.35 and 109.33 ppm were assigned to C-3′ and C-4′ carbon of furan moiety, while the signals at 153.03 and 162.04 ppm were assigned to C-2′ and C-5′ carbon of furan moiety, respectively. Another signal at 151.09 ppm was due to C-1‴ of phenyl ring and the signal appeared at 131.73 ppm was due to furan ring attached to phenyl ring of the electronegativity substituent. The aromatic carbons were observed in the region of 115.76-129.07 ppm . Therefore, with reference to FT-IR, ^1H & ^{13}C NMR spectral studies in compound **5a**, the tentative assignments made for the title compounds are confirmed.

Antimicrobial activity: The antimicrobial potential of synthesized molecules was determined by disc diffusion method. The antibacterial activity was determined against Gram-positive bacteria: *Staphylococcus aureus*, *Steptococcus pygenes* and Gram-negative bacteria: *Escherichia coli* and *Pseudomonas aeruginosa* and compared to positive control ciprofloxacin drug. The fungal study of compounds was carried out against fungal strain: *Candida albicans* and compared to positive control clotrimazole drug. The results of antibacterial and antifungal were evaluated in terms of millimeter and the results are shown in Table-1.

*C*ompounds **5b** and **5g** have better zone of inhibition (22 mm and 21 mm) against *S. pyogenes*. Compound **5h** exihibited a best zone of inhibition (19 mm) among the eight compounds against *S. aureus*. Compounds **5b**, **5c** and **5h** have good zone of inhibition (28, 19, 21 mm) against *E. coli* strain. Compound **5g** also exhibited a good zone of inhibition (24 mm) against *P. aeruginosa*. All the compounds **5a-h** have an moderate to good activity against all the bacterial stains like Gram-positive and Gram-negative bacteria. Compound **5h** has better zone of inhibition (17 mm) against the fungal strain *Candida albicans* when compared with the standard drug clotrimazole. From *in vitro* antimicrobial results, compound containing an electronegativity substitution like (F, Cl and NO_2 group) exhibits good activity compared with standard drug (ciprofloxacin).

Molecular docking studies

Using bacterial protein: The synthesized pyrazoline compounds (**5a-h**) were subjected to *in silico* docking study using and breast cancer protein (1OQA) and bacterial protein (1UAG).

TABLE-1
ANTIMICROBIAL SCREENING RESULTS OF SYNTHESIZED 4-CHLOROPHENYL FURFURAL BEARING PYRAZOLE MOLECULES (**5a-h**)

Compound	Bacterial strain				Fungal strain
	Gram-positive		Gram-negative		
	Staphylococcus aureus	*Steptococcus pyogenes*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*
5a	11	10	13	12	11
5b	18	22	28	16	13
5c	16	10	19	15	09
5d	11	10	10	09	07
5e	13	12	10	11	09
5f	12	15	10	10	12
5g	16	21	17	24	14
5h	19	18	21	20	17
Ciprofloxacin	26	19	17	22	–
Clotrimazole	–	–	–	–	24

This protein was downloaded from protein data bank file. The docking results are shown in Table-2. The results of molecular docking study revealed that all synthesized compounds show high binding affinity score when compared with standard drugs especially, synthesized compound **5h** shows high binding affinity score (-9.7 kcal/mol) compared with standard drug, ciprofloxacin. This compound has one conventional hydrogen bond interaction formed with the amino residue is LEU: 299 and also this compound have one hydrophobic interaction formed with the amino residue is LEU: 333. Hydrophobic interaction and conventional hydrogen bond interactions of the other compounds are shown in Table-2. The 3D and and 2D images of compound **5h** are shown in Fig. 1.

Using breast cancer protein: Synthesized novel pyrazoline compounds (**5a-h**) were subjected to *in silico* docking study using breast cancer protein 1OQA. This protein was downloaded from Protein Data Bank file. The docking results are shown in Table-3. From these results, all the synthesized compounds have good BAS. Especially, compound **5h** have one C-V-B interaction formed with the amino residue is ASP: 65 and also this compound have two H-P interaction formed with the amino residue is PRO: 59 and PRO: 103.The docking score and the hydrophobic interactions of other compounds are given in Table-3. The 2D and 3D images of compound **5h** are shown in Fig. 2.

***in silico* ADME property:** Determination of ADME parameters of the synthesized 1-(3-(5-(4-chlorophenyl)furan-2-yl)-5-aryl-4,5-dihydropyrazol-1-yl)ethanone derivatives (**5a-h**) were done using SwissADME and Molinspiration online softwares. The success of a drug is determined not only by good efficacy but also by an acceptable ADME (absorption, distribution, metabolism and excretion) profile. In the present study, we have calculated log $p_{o/w}$, solubility (logs), molecular weight, TPSA (topological polar surface area), drug-likeness, hydrogen bond acceptor, hydrogen bond donor, molar refractivity, drug score and pharmacokinetics study of GI absorption,

TABLE-2
in silico MOLECULAR DOCKING STUDY WAS CARRIED OUT USING BACTERIAL PROTEIN (1UAG)

Compound	R (substitution)	Score (kcal/mol)	H-bond interaction	Hydrophobic interaction
5a	H	-9.2	LEU : 299	LEU : 333
5b	F	-9.4	LEU : 299	LEU : 333
5c	Br	-9.2	LEU : 299	LEU : 333
5d	CH_3	-9.4	LEU : 299	LEU : 333
5e	OCH_3	-9.1	LEU : 299	LEU : 333
5f	C_6H_5	-9.5	LEU : 416, SER: 415	ALA : 414, LEU : 416
5g	Cl	-9.4	LEU : 299	LEU : 333
5h	NO_2	-9.7	LEU : 299	LEU : 333
Ciprofloxacin	–	-7.8	LEU : 416, SER : 415, HIS : 183, LYS : 115, LYS : 319	LYS : 319, PHE : 422

TABLE-3
in silico DOCKING STUDY WAS CARRIED OUT FOR SYNTHESIZED COMPOUND (**5a-h**) USING BREAST CANCER PROTEIN 1OQA

Compound	R (Substitution)	Docking score	H-Bond interaction	Hydrophobic interaction
5a	H	-7.0	–	PRO : 103, PRO : 59, ILE : 102
5b	F	-7.4	–	VAL : 38, CYS : 15, PRO : 18
5c	Br	-7.0	–	PRO : 103, PRO : 59
5d	CH_3	-7.1	–	PRO : 78, ILE : 102, CYS : 94, LEU : 101
5e	OCH_3	-6.8	–	CYS : 94, PRO :78, LEU : 101, LEU : 97
5f	C_6H_5	-7.4	–	LYS : 40, PRO : 18
5g	Cl	-7.0	–	PRO : 103, PRO : 59
5h	NO_2	-7.9	ASP : 65	PRO : 59, PRO : 103

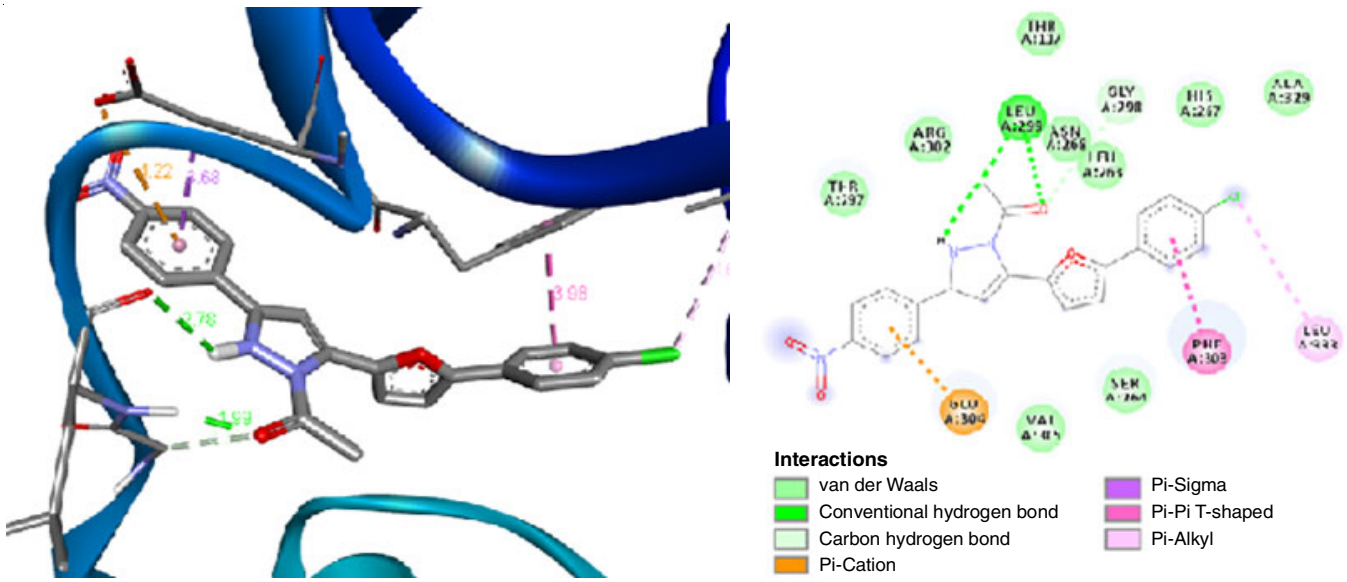


Fig. 1. 2D and 3D images of compound **5h** docked with 1UAG protein

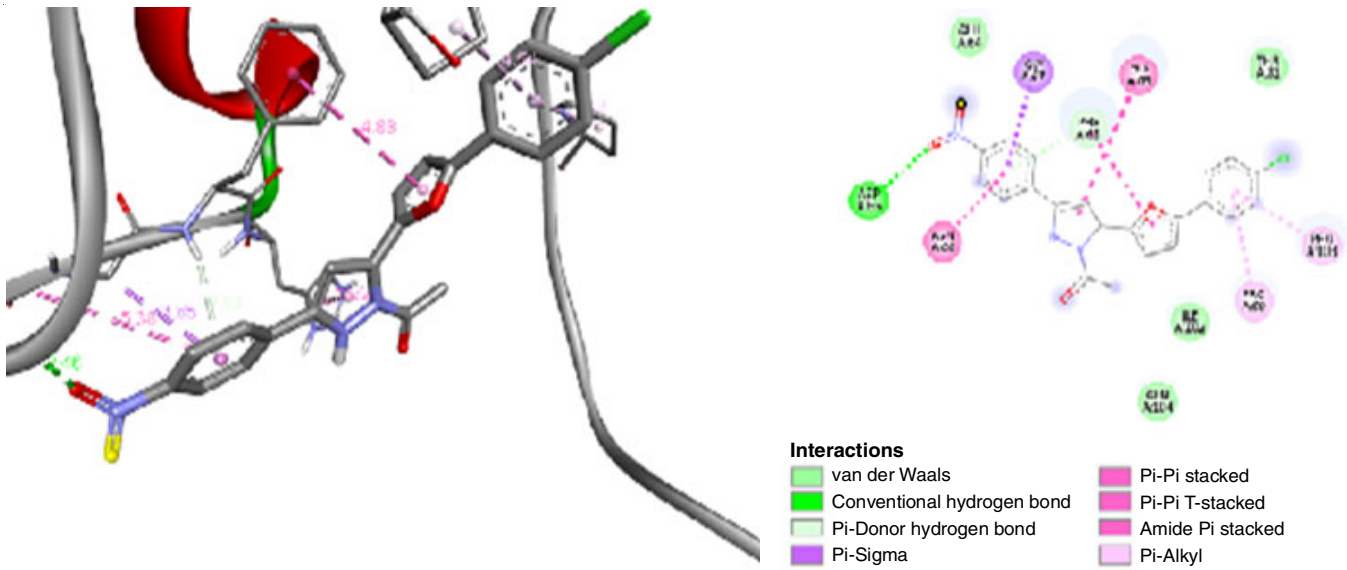


Fig. 2. 2D and 3D images of compound **5h** docked with 1OQA protein

BBB (blood brain barrier), P-gp substrate, cytochrome P450 family and sub-family members and log kp (skin permeation), Lipinski′s violation, Ghose filter,Veber, Egan, Muegge and Bioavailability score, Pains, Brenk, lead-likeness and synthetic accessibility were carried using swissADME online tool. Likewise, we have calculated the terms using Molinspiration online property toolkit [44,43]. The absorption (% ABS) was calculated [45] as follows:

$$\% \text{ ABS} = 109 - (0.345 \times \text{TPSA})$$

All the 4-chlorophenyl furfural derivatives (**5a-h**) were subjected to ADME property prediction with the help of SwissADME online software. This *in silico* method plays a major role in the pharmacokinetic property of the new molecules. All the target compounds obey the Lipinski rule of five and also exhibit good solubility and absorption values. Especially, compound **5h** shows better TPSA values compared than other compounds. The compound **5h** also exhibits good log P value. The ADME prediction values of other compounds are shown in Table-4.

Pharmacokinetics and drug-likeness prediction by Swiss ADME: The pharmacokinetic properties and drug-likeness prediction of the synthesized compounds (**5a-h**) were performed by SwissADME online version and molinspiration online software data are given in Tables 5 and 6. According to pharmacokinetic properties, all the synthesized compounds showed a high gastrointestinal (GI) absorption. All compounds have BBB permeability except compound **5h**, which has low permeability. However, most of them showed inhibition to cytochrome P450 isomers (CYPIA2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4). The drug-likeness prediction was conducted depending on the selected Lipinski′s, Ghose and veber rules and bioavailability score. The Lipinski′s rule of five states that the absorption or permeation of a molecule is more likely when the molecular weight is under 500 g/mol, the value of log P is lower than 5, and the molecule has utmost 5 H-donor and 10 H-acceptor. Ghose filter

TABLE-4
ADME PREDICTION VALUES OF 4-CHLOROPHENYL FURFURAL PYRAZOLE DERIVATIVES (**5a-h**) USING SWISSADME ONLINE TOOL

Compound	R (substitution)	log P	Solubility log S	m.w.	TPSA	Drug likeness	Hy-A	Hy-D	Drug-score	Molar refractivity
Rule	–	< 5	–	< 500	–	–	< 10	< 5	–	–
5a	H	3.71	-5.09	364.82	45.81	7.25	3	0	0.71	109.74
5b	F	3.81	-5.24	382.82	45.81	7.01	4	0	0.68	109.70
5c	Br	4.11	-5.99	443.73	45.81	5.67	3	0	0.55	111.44
5d	CH_3	4.02	-5.38	378.86	45.81	5.73	3	0	0.66	114.71
5e	OCH_3	3.98	-5.15	394.86	55.04	7.18	4	0	0.70	116.23
5f	C_6H_5	4.38	-6.57	440.93	45.81	4.03	3	0	0.53	135.18
5g	Cl	3.99	-5.68	399.28	45.81	7.90	3	0	0.61	114.75
5h	NO_2	3.44	-5.14	409.83	91.63	-3.00	5	0	0.40	118.56

defines drug-likeness constraints as follows: calculated log P is between 3.71 and 4.38, m.w. is between 364 and 444, molar refractivity is between 109 and 135, and the total number of atoms is between 24 and 32. Veber rule defines drug-likeness constrains as Rotatable bond count ≤ 10 and polar surface area (PSA) ≤ 140. All compounds have the similar bioavailability score of 0.55. Screening process with Lipinski′s rule of Five showed that there were only six compounds (**5a**, **5b**, **5c**, **5d**, **5e** and **5h**) meet the criteria of drug likeness assessment however, compounds **5f** and **5g** were rejected with one violation *i.e.* MLOGp > 4.5 (Table-7). According to the screening process with Ghose rules showed that seven compounds were meet the criteria except compound **5f**. The compound has two violations *i.e.* WLOGP > 5.6, MR > 130. However, the screening process with Veber rules, all compounds meets the criteria of drug-likeness assessment. Medicinal chemistry properties also carried out by Molinspiration software. In these study, they have no alert in Pains and Brenk but in compound **5h** showed one violation. In lead likeness properties, all synthesized compounds **5a-h** showed two violations *viz.* molecular weight >350, and XLOGP3 > 3.5. All the compounds have the synthetic ability value between 3.97-4.34. From these values of synthetic ability, the synthesized compounds (**5a-h**) obeyed the medicinal chemistry property. The values are given in Table-7.

TABLE-5
PHARMACOKINETICS STUDY FOR THE SYNTHESIZED COMPOUNDS **5a-h** BY SWISSADME

Compound	Gastro intestinal absorption	Blood brain barrier per meant	P-glycoprotein substrate	CYPIA2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6	CYP3A4	log kp Skin permiation (cm/s)
5a	High	Yes	No	Yes	Yes	Yes	No	Yes	-5.41
5b	High	Yes	No	Yes	Yes	Yes	No	Yes	-5.45
5c	High	Yes	No	Yes	Yes	Yes	No	No	-5.40
5d	High	Yes	No	No	Yes	Yes	No	Yes	-5.24
5e	High	Yes	No	Yes	Yes	Yes	No	Yes	-5.61
5f	High	Yes	No	No	No	Yes	No	Yes	-4.72
5g	High	Yes	No	Yes	Yes	Yes	No	Yes	-5.17
5h	High	No	No	Yes	Yes	Yes	No	Yes	-5.80

CYP1A2-Cytochrome P450 family 1 Subfamily A member 2(PDB:2H14); CYP2C19-Cytochrome P450 family 2-Subfamily C member 19 (PDB); CYP2C9-Cytochrome P450 family 2-Subfamily C member 9 (PDB); CYP2D6-Cytochrome P450 family 2-Subfamily D member 6(PDB:5TFT); CYP3A4-Cytochrome P450 family 3-subfamily A member 4 (PDB)

TABLE-6
ADDITIONAL PHYSIO-CHEMICAL PARAMETERS OF COMPOUNDS **5a-h** WAS CALCULATED USING MOLINSPIRATION SOFTWARE

Compound	% ABS	n atoms	TSPA	n-rot b	m.w.	MV	milog P	n-OHNH	n-OH	Lipinski's Violation
5a	93.2	26	45.81	3	364.83	316.34	4.78	0	4	0
5b	93.2	27	45.81	3	382.82	321.27	4.94	0	4	0
5c	93.2	27	45.81	3	443.73	334.23	5.59	0	4	1
5d	93.2	27	45.81	3	378.86	332.90	5.23	0	4	1
5e	90.01	28	55.05	4	394.86	341.89	4.83	0	5	0
5f	93.2	32	45.81	4	440.93	387.75	6.57	0	4	1
5g	93.2	27	45.81	3	399.28	329.88	5.46	0	4	1
5h	77.39	29	91.64	4	409.83	339.68	4.74	0	7	0
Std1	83.29	24	74.54	3	331.35	285.46	-0.70	2	6	0
Std2	102.85	25	17.83	4	344.85	344.85	547	0	2	1

% ABS – absorption; n atoms – Number of atoms; TSPA - Topological polar surface area; n-rotb - Number of rotational bonds; MV -Molecular volume; milog P - Octanol-water partition coefficient; n-OHNH- Hydrogen bond acceptor; n-OH - Hydrogen bond donor

TABLE-7
DRUG LIKENESS PROPERTIES FOR THE SYNTHESIZED COMPOUNDS **5a-h**

Comd.	Drug likeness						Medicinal Chemistry			
	Lipinski's	Ghose	Veber	Egan	Muegge	Bioavail-ability	Pains	Brenk	Leadlikeness	Synthetic accessibility
5a	Yes: 0-Violation	Yes	Yes	Yes	Yes	0.55	0-alert	0-alert	No:2-Violation, MW > 350, XLOGP3 > 3.5	3.97
5b	Yes:0-Violation	Yes	Yes	Yes	Yes	0.55	0-alert	0-alert	No:2-Violation, MW > 350,XLOGP3 > 3.5	3.97
5c	Yes:0-Violation	Yes	Yes	Yes	No:1-Violation XLOGP3 > 5	0.55	0-alert	0-alert	No:2-Violation, MW > 350, XLOGP3 > 3.5	3.97
5d	Yes:0-Violation	Yes	Yes	Yes	Yes	0.55	0-alert	0-alert	No:2-Violation, MW > 350, XLOGP3 > 3.5	4.08
5e	Yes:0-Violation	Yes	Yes	Yes	Yes	0.55	0-alert	0-alert	No:2-Violation, MW > 350, XLOGP3 > 3.5	4.02
5f	Yes:1-Violation MLOGP > 4.15	No:2-Violation WLOGP > 5.6, MR > 130	Yes	Yes	No:1-Violation XLOGP3 > 5	0.55	0-alert	0-alert	No:2-Violation, MW > 350, XLOGP3 > 3.5	4.34
5g	Yes:1-Violation MLOGP > 4.15	Yes	Yes	Yes	No:1-Violation XLOGP3 > 5	0.55	0-alert	0-alert	No:2-Violation, MW > 350,XLOGP3 > 3.5	3.97
5h	Yes:0-Violation	Yes	Yes	Yes	Yes	0.55	0-alert	1-alert, Nitro group	No:2-Violation, MW > 350, XLOGP3 > 3.5	3.99

Bioactivity score: The previous results showed that some of the compounds have physiochemical properties within the acceptable criteria. By using Molinspiration software "online test", the bioactivity of all compounds were estimated and represented in Table-8. The bioactivity scores of the synthesized compounds indicated the probability of good to moderate activity towards GCPR ligand, ion channel modulators, kinase inhibitor, nuclear receptor ligands, protease inhibitor and other enzyme inhibitors. These scores for organic molecules can be interpreted as active (bioactivity score > 0), moderately active (bioactive score: -5.0-0.0) and inactive (bioactivity score < -5.0) [46]. In GCPR ligand inter-actions, compounds **5b**, **5f** and **5g** have moderately active against the standard drugs.

Conclusion

In this work, a novel 4-chlorophenyl furfural pyrazole derivatives (**5a-h**) were synthesized *via* nucleophilic addition reaction. The chemical structure of the target molecules were characterized using FT-IR, ^{1}H & ^{13}C NMR spectral analysis. The synthesized compounds showed an excellent docking score compared with ciprofloxacin. In the results of *in silico* ADME property, compound **5h** shows good TPSA value of 91.63 compared with other synthesized compounds, but compound **5g** shows good TPSA (55.04), good drug score (0.61), good solubility (-6.55) and good drug-likeness score (7.90) compared with other synthesized compounds. Drug-likeness properties and medicinal chemistry properties criteria were also carried out for the synthesized compounds and most of them were met the criteria. Antimicrobial activity was evaluated for synthesized 4-chlorophenyl furfural pyrazole derivatives, where compounds **5b**, **5g** and **5h** showed an excellent activity against some microorganisms.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

TABLE-8
BIOACTIVITY SCORE OF FURFURYL PYRAZOLE DERIVATIVES BY MOLINSPIRATION ONLINE TOOL

Compound No.	G-protein coupled receptor ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
5a	-0.51	-1.05	-0.82	-0.69	-0.64	-0.41
5b	-0.49	-1.02	-0.76	-0.65	-0.65	-0.41
5c	-0.59	-1.08	-0.83	-0.77	-0.73	-0.46
5d	-0.53	-1.07	-0.82	-0.70	-0.68	-0.44
5e	-0.52	-1.04	-0.79	-0.66	-0.66	-0.42
5f	-0.40	-0.84	-0.64	-0.54	-0.51	-0.31
5g	-0.49	-1.01	-0.79	-0.67	-0.62	-0.39
5h	-0.60	-0.99	-0.86	-0.71	-0.72	-0.46
Ciprofloxacin	0.12	-0.04	-0.07	-0.19	-2.0	-0.28
Clorimazole	0.17	0.30	0.14	-0.21	-0.13	0.42

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